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(54) **The acetic acid ester of haloperidol and pharmaceutical compositions thereof.**

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(56) References cited:
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US-A- 3 438 991

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Description

The present invention relates to the novel acetic acid ester of 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone, as well as pharmaceutically acceptable acid addition salts thereof, a method of preparation, pharmaceutical compositions and a method of treating psychoses by administering said ester to an animal or human body. The compound 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone, known as haloperidol (INN), has for many years been a widely used neuroleptic in the treatment of severe psychotic conditions including schizophrenic disorders. So far, haloperidol has been administered orally or in form of aqueous solutions for injection containing haloperidol and lactic acid. Moreover, a very long acting depot preparation consisting of the decanoic acid ester of haloperidol in sesame oil is known from GB-A-2054371. US-A-3,408,356 discloses generically some long chain esters of haloperidol which are useful as long acting tranquilizers. The aqueous solution for injection, containing haloperidol and lactic acid, which is relatively short acting and used in the acute phase, has however in most cases very serious side effects at the site of injection in the form of necrosis of the muscle tissue. The long acting haloperidol decanoate preparation of GB-A-2054371 is free from such side effects.

Accordingly, there has been a need for short acting injectable preparations of haloperidol causing less damage of the muscle tissue.

It has now according to the present invention been found that by substituting the aqueous solutions of haloperidol with solutions in pharmaceutically acceptable oils of the so far unknown acetic acid ester of haloperidol, or a pharmaceutically acceptable acid addition salt thereof, practically no damage of muscle tissue occured, at the same time as a reasonably rapid onset of antipsychotic effect was obtained, lasting for 2-7 days.

The compositions of the present invention are prepared by dissolving or suspending the acetic acid ester of haloperidol, or a pharmaceutically acceptable acid addition salt thereof, in a pharmaceutically acceptable oil under sterile conditions. The preferred oils are of vegetable origin such as peanut oil, sesame oil, cotton seed oil, corn oil, soybean oil, olive oil and most preferably light vegetable oil.

According to the method of the invention haloperidol is reacted with a reactive derivative of acetic acid in a solvent and isolated in the form of the free base or a pharmaceutically acceptable acid addition salt thereof.

As reactive derivatives of acetic acid may especially be mentioned the anhydride or an acetylhalide, preferably the chloride.

The solvent used in the reaction may advantageously be pyridine or an inert solvent containing an acid binding agent.

The reaction may preferably be carried out at elevated temperature such as reflux temperature.

This invention also includes pharmaceutically acceptable salts of the acetic acid ester of 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Examplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts, which is wellknown to the art.

The method of the invention shall in the following be illustrated with some examples which may not be construed as limiting for the scope of the invention:

EXAMPLE 1

4-(4-Acetoxy-4-(4-chlorophenyl)-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone (Haloperidol-acetate)

4-(4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone (20 g) and acetic acid anhydride (16 g) in 200 ml of dried pyridine (KOH pellets) were refluxed for 2 h. The mixture was poured into cold H_2O (0 °C) (2 liters) and extracted with isopropylether (2 x 200 ml). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated. The title compound was obtained after column chromatog-

raphy on silica gel (eluent, ethyl acetate/dichloromethane/methanol, 1:1:1). Yield 10.6 g (48%). Mp 106-110 °C (from isopropyl ether). The hydrochloride salt was precipitated from acetone. Mp 215 °C. According to TLC analysis the content of Haloperidol was 0.5%.

The following examples of formulations illustrate the compositions of the present invention:

EXAMPLE 2

Haloperidol acetate Thin vegetable oil BP(Viscoleo(R))	5 grams ad 100m ml

EXAMPLE 3

Haloperidol acetate Sesame oil BP	2 grams ad 100 ml

EXAMPLE 4

Haloperidol acetate Thin vegetable oil BP	3 grams ad 100 ml

EXAMPLE 5

Haloperidol acetate Olive oil	10 grams ad 100 ml

EXAMPLE 6

Haloperidol acetate Sesame oil BP	5 grams ad 100 ml

The solutions according to Examples 2 - 6 are made under sterile conditions and filled into suitable receptacles such as ampoules or vials, each containing 1 - 3 ml solution.

The compositions of the present invention are preferably administered in unit dosage form in ampoules or vials, the solution or suspension containing from about 1 mg to about 100 mg of active ingredient per ml of solution or suspension.

Some of the above compositions of Example 2 - 6 were tested for the ability to protect dogs against vomiting caused by apomorphine. The test has been described by Janssen, P.A.J., Niemegeers, C.J.E. and K.H.L. Scheelekens, Arzneimittel-Forschung, 1965, 15, 1196-1201.

It was found that a good protection was achieved compared with corresponding injections of aqueous solutions of unesterified haloperidol.

The local toxicity at the injection site was tested in pigs. 2ml of test solution were injected intramuscularly. Three days after injection the pigs were anaesthetized and killed by exsanguination. Macroscopic changes at the injection site were noted, and the quantity of the damaged or depleted muscle tissue was determined by measurement of depletion of creatinphosphokinase (CK). Whereas the composi-

tions of the present invention showed only slight depletions of CK in about 0.15 - 0.40 g of muscle tissue with almost no macrosopic findings, the corresponding test with a commercial 0.5% aqueous solution of haloperidol as the lactate showed depletion of CK in about 6 g of muscle tissue with pronounced macrosopic findings of necrotic muscle tissue sharply demarcated from surrounding healthy tissue.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain psychic abnormalities of animals by administering to a living animal body, including human beings, an adequate quantity of a composition according to the present invention. An adequate quantity would be from about 0.005 mg to about 1 mg per kilo of body weight in each injection dosis.

It is to be understood that the invention is not limited to the exact details of operation or exact compound or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LH, NL, SE

1. The acetic acid ester of 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-butanone, or pharmaceutically aceptable acid addition salts thereof.

2. The acetic acid ester of 4-(4-(4-chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-butanone.

3. An injectable pharmaceutical composition containing as an active ingredient an effective amount of a compound of Claim 1 or 2, and as a carrier a pharmaceutically acceptable oil possibly together with other pharmaceutically acceptable adjuvants or excipients.

4. A pharmceutical composition according to Claim 3, wherein the active ingredient is the compound of Claim 2.

5. A pharmaceutical composition according to Claim 3 or 4, in unit dosage form wherein the active ingredient is present in an amount of from 1 mg to 100 mg per ml of solution or suspension.

6. A pharmaceutical composition according to any of Claims 3 - 5, wherein the oil is sesame oil.

7. A pharmaceutical composition according to any of Claims 3 - 5, wherein the oil is thin vegetable oil BP.

8. A method for the preparation of the active acid ester of 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone, or a pharmaceutically accetable acid addition salt thereof, comprising treating 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone with a reactive derivative of acetic acid, and isolating the said acetic acid ester in the form of the free base or a pharmaceutically acceptable acid addition salt thereof.

9. The method of Claim 8, wherein the reactive derivative of acetic acid is the acid chloride.

Claims for the following Contracting States : AT, ES, GR

1. A method for the preparation of the acetic acid ester of 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone, or a pharmaceutically acceptable acid addition salt thereof, comprising treating 4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone with a reactive derivative of acetic acid, and isolating the said acetic acid ester in the form of the free base or a pharmaceutically acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the reactive derivative of acetic acid is the acid chloride.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LH, NL, SE

1. Essigsäureester von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-butanon oder Pharmakologisch unbedenkliche Säureadditionssalze davon.

2. Der Essigsäureester von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-butanon.

3. Injizierbare pharmazeutische Zubereitung, enthaltend als aktiven Wirkstoff eine wirksame Menge einer Verbindung nach Anspruch 1 oder 2, und als Träger ein pharmakologisch unbedenkliches Öl, gegebenenfalls zusammen mit anderen pharmazeutisch unbedenklichen Adjuvantien oder Excipienten.

4. Pharmazeutische Zubereitung nach Anspruch 3, wobei der aktive Wirkstoff die Verbindung von Anspruch 2 ist.

5. Pharmazeutische Zubereitung nach Anspruch 3 oder 4, in Dosierungseinheitsform, wobei der aktive Wirkstoff in einer Menge von 1 mg bis 100 mg je ml Lösung oder Suspension vorliegt.

6. Pharmazeutische Zubereitung nach den Ansprüchen 3-5, wobei das Öl Sesamöl ist.

7. Pharmazeutische Zubereitung nach den Ansprüchen 3-5, wobei das Öl ein dünnes Pflanzenöl BP ist.

8. Verfahren zur Herstellung des aktiven Säureesters von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-1-butanon oder einem pharmakologisch unbedenklichen Säureadditionssalz davon, gekennzeichnet durch Behandeln von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-1-butanon mit einem reaktiven Derivat von Essigsäure und Isolierung des Essigsäureesters in Form der freien Base oder eines Pharmakologisch unbedenklichen Säureadditionssalzes davon.

9. Verfahren nach Anspruch 8, wobei das reaktive Derivat der Essigsäure das Säurechlorid ist.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung des Essigsäureesters von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-1-butanon oder einem pharmakologisch unbedenklichen Säureadditionssalz davon, gekennzeichnet durch Behandeln von 4-(4-(4-Chlorphenyl)-4-hydroxy-1-piperidinyl)-1-(4-fluorphenyl)-1-butanon mit einem reaktiven Derivat der Essigsäure und Isolieren des erhaltenen Essigesters in Form der freien Base oder eines pharmakologisch unbedenklichen Säureadditionssalzes davon.

2. Verfahren nach Anspruch 1, wobei das reaktive Derivat der Essigsäure das Säurechlorid ist.

Revendications
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Ester de l'acide acétique de la 4-(4-(4-chlorophényl-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone ou ses sels d'addition d'acide pharmaceutiquement compatibles.

2. Ester de l'acide acétique de la 4-(4-(4-chlorophényl)-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone.

3. Composition pharmaceutique injectable contenant en tant qu'ingrédient actif une quantité efficace d'un composé selon la revendication 1 ou 2, et en tant que véhicule une huile pharmaceutiquement compatible éventuellement avec d'autres adjuvants ou excipients pharmaceutiquement compatibles.

4. Composition pharmaceutique selon la revendication 3, dans laquelle l'ingrédient actif est le composé de la revendication 2.

5. Composition pharmaceutique selon la revendication 3 ou 4, sous forme de dosage unitaire dans laquelle l'ingrédient actif est présent dans une quantité allant de 1 mg à 100 mg par ml de solution ou de suspension.

6. Composition pharmaceutique selon l'une quelconque des revendications 3 - 5, dans laquelle l'huile est de l'huile de sésame.

7. Composition pharmaceutique selon l'une quelconque des revendications 3 - 5, dans laquelle l'huile est de l'huile végétale fine BP.

8. Procédé pour la préparation de l'ester de l'acide actif de la 4-(4-(4-chlorophényl)-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone ou son sel d'addition d'acide pharmaceutiquement compatible, comprenant le traitement de la 4-(4-(4-chlorophényl)-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone avec un dérivé réactif de l'acide acétique, et l'isolation de l'ester de l'acide acétique sous la forme de la base libre ou son sel d'addition d'acide pharmaceutiquement compatible.

9. Procédé selon la revendication 8, dans lequel le dérivé réactif de l'acide acétique et le chlorure d'acide.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé pour la préparation de l'ester de l'acide acétique de la 4-(4-(4-chlorophényl)-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone, ou son sel d'addition d'acide pharmaceutiquement compatible, comprenant le traitement de la 4-(4-(4-chlorophényl)-4-hydroxy-1-pipéridinyl)-1-(4-fluorophényl)-butanone avec un dérivé réactif de l'acide acétique, et l'isolation de l'ester de l'acide acétique sous la forme de base libre ou son sel d'addition d'acide pharmaceutiquement compatible.

2. Procédé selon la revendication 1, dans lequel le dérivé réactif de l'acide acétique et le chlorure d'acide.